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Anion Transfer Reactions from Chiral Hypervalent Iodine Macrocycles

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Abstract

The direct chlorination, bromination and azidation of beta keto esters, 2-acetyl-1-tetralone and methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate is achieved utilizing anion-coordinated hypervalent iodine benziodazoles derived from hypervalent iodine macrocycles. This reaction, which introduces the halogen, azido or cyano group at the alpha carbon atom of beta keto esters, is accomplished in chloroform at 60 °C and results in the formation of a chiral center. Depending on the structure of the benziodazole reagent, the reaction can have mild enantioselectivity. The reaction between 2-acetyl-1-tetralone and phenylalanine-derived hypervalent iodine benziodazoles results in the chlorinated product with 26% enantiomeric excess.

Keywords: hypervalent iodine; asymmetric; halogenation; azidation

1. Introduction

Azide, cyano and halogen groups are important functionalities in organic chemistry. For example, the insertion of cyano groups in different organic compounds is pivotal in modern synthetic chemistry as it stands as a significant functional group in several natural products [1], pharmaceuticals [2] and materials [3]. Organoazide compounds have received considerable attention from the scientific community owing to their use in industrial-scale synthesis of heterocycles such as triazole and tetrazole [4]. Additionally, organic azides serve as the energy-rich molecules and flexible intermediates in organic chemistry [5]. Similarly, many pharmaceutical drugs consist of halogenated organic structures [6]. Halogenated organic compounds have emerged as structures of great interest owing to their applications as dyes, flame retardants, imaging agents in medical diagnosis and in materials science [7]. Traditional synthetic methods to prepare cyano, azido and halo compounds often rely on the use of hazardous chemical reagents like sodium cyanide, sodium azide and H-X (X = F, Cl, Br). These reactions not only pose safety risks in the laboratory but also cause harmful effects on the environment upon disposal. Therefore, there is a growing need to find alternative strategies as safer, sustainable and cost-effective approaches for the large-scale production of these functionalized compounds.

In general, nucleophilic substitution of RX (X = leaving group) with inorganic cyanide, azide and halide has been widely used in research laboratories as well as in industry to synthesize organic cyanide, organic azide and organic halide, respectively. In addition, significant achievements have been made in recent decades towards nucleophilic addition of cyanides to electrophiles for the synthesis of cyano compounds; the reaction of the corresponding aliphatic amine with triflyl azide (TfN_3) to synthesize organic azides [8];

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and reactions involving N-bromosuccinimide (NBS), N-fluorobenzenesulfonimide (NFSI) and diethylaminosulfur trifluoride (DAST) as halogenating agents to synthesize organic halides [7]. As an alternative, cyanation, azidation and halogenation of α-functionalization of carbonyl compounds can also lead to the synthesis of large numbers of interesting synthetic building blocks and molecules [9]. Several groups have reported the direct halogenation, cyanation and azidation of beta keto esters using hypervalent iodine reagents in an enantioselective manner [9,10]. However, very little is known about the benziadazole-based tetracoordinated hypervalent iodine species featuring an I-X bond (X = F, Cl, Br, CN, N3) for the direct cyanation, halogenation and azidation of beta keto esters. Herein, we have demonstrated direct azidation and halogenation with a new chiral hypervalent iodine reagent in 2-acetyl-1-tetralone and methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate systems.

2. Materials and Methods

Unless otherwise noted, all reagents were used as received and all reactions were carried out under an argon atmosphere. Column chromatography was performed on a CombiFlash® Rf system with Redisep normal-phase silica columns (Teledyne ISCO Inc., Lincoln, NE, USA). ^{1}H NMR and ^{13}C NMR were recorded on a Varian 400 MHz or JEOL 500 MHz NMR workstation at room temperature, unless otherwise noted.

2.1. General Procedure for the Chlorination, Azidation and Bromination of 2-Acetyl-1-Tetralone

In a 20 mL round-bottom flask, 2-acetyl-1-tetralone (0.23 mmol, 1 eq.) was dissolved in 5 mL $CHCl_3$. A freshly prepared adduct solution (**2a-c**, **3a-c**) was prepared from mixing precursor **1a** or **1b** (0.20 mmol–0.6 mmol of monomer, 2.6 eq.) and tetrabutylammonium salt (0.60 mmol, 2.6 eq.) in 5 mL $CHCl_3$. The adduct solutions were added at room temperature to the round-bottom flask. The reaction mixture was sonicated to make the solution homogenous and then stirred at 60 °C for 4-48 h. After completion of the reaction, the solvent was evaporated to give a solid that was purified using column chromatography with 90:10 hexane/ethyl acetate to give **6a-c**.

1-(2-chloro-1-hydroxy-1,2,3,4-tetrahydronapthalen-2-yl) ethenone (**6a**): 2-Acetyl 1-tetralone (43.3 mg, 0.23 mmol), **1a** (234 mg, 0.20 mmol) and tetrabutyl ammonium chloride (99 mg, 0.60 mmol) gave **6a** (29 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.3 Hz, 1H), 3.33–3.20 (m, 1H), 3.09–3.00 (m, 1H), 2.95–2.87 (m, 1H), 2.52 (s, 3H) and 2.44–2.37 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 201.9, 189.9, 142.9, 134.6, 130.1, 128.9, 128.8, 127.3, 73.9, 33.5, 27.7 and 25.7. HRMS(ES+): m/z for $C_{12}H_{12}O_2Cl$. Calc: 223.0526, found: 223.0527.

1-(2-azido-1-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl) ethenone (**6b**) 2-Acetyl 1-tetralone (43.3 mg, 0.23 mmol), **1a** (234 mg, 0.20 mmol) and tetrabutyl ammonium azide (170 mg, 0.60 mmol) gave **6b** (32 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 3.22–3.10 (m, 1H), 3.00–2.90 (m, 1H), 2.59–2.51 (m, 1H), 2.30 (s, 3H) and 2.21–2.15 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 202.4, 191.0, 143.3, 134.8, 130.4, 128.8, 128.4, 127.3, 75.5, 30.5, 26.5 and 24.9. HRMS(ES+): m/z for $C_{12}H_{12}O_2N$ [M-N2+H] + Calc: 202.0868, found: 208.0873.

1-(2-Bromo-1-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-ethanone (**6c**) 2-Acetyl 1-tetralone (43.3 mg, 0.23 mmol), **1a** (234 mg, 0.10 mmol) and tetrabutyl ammonium bromide (194 mg, 0.60 mmol) gave **6c** (25 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 3.27–3.15 (m, 1H), 3.10–3.02 (m, 1H), 2.89–2.80 (m, 1H), 2.61 (s, 3H) and 2.52–2.44 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 200.7, 189.7, 142.7, 134.4, 129.9, 128.8, 128.8, 127.2, 68.3, 33.8, 28.3 and 26.8. HRMS(ES+): m/z for $C_{12}H_{12}O_2Br$ [M+H] + Calc: 267.0021, found: 267.0021.

2-acetyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbonitrile (**6d**) 2-Acetyl 1-tetralone (43.3 mg, 0.23 mmol), **1a** (234 mg, 0.20 mmol) and tetrabutyl ammonium cyanide (161 mg, 0.60 mmol) gave **6d** (15 mg, 30%). ^{1}H NMR (400 MHz, CDCl3) δ 8.08 (d, J = 7.8 Hz, 1H), 7.59 (td, J = 7.5, 1.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.38–7.33 (m, 1H), 3.40 (ddd, J = 17.5, 13.3, 4.4 Hz, 1H), 3.22 (ddd, J = 17.2, 4.9, 2.7 Hz, 1H), 2.84 (td, J = 13.5, 4.9 Hz, 1H), 2.36 (ddd, J = 13.9, 4.5, 2.6 Hz, 1H) and 1.65 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 189.3, 143.0, 135.0, 132.5, 129.1, 127.9, 127.3, 117.0, 67.0, 54.4, 30.3, 29.7 and 28.0. HRMS(EI+): *m*/*z* for $C_{13}H_{11}O_2N$ [M] + Calc: 213.0789, found: 213.0787.

2.2. General Procedure for the Chlorination, Azidation and Bromination of the Methyl 1-Oxo-2,3-Dihydro-1H-Indene-2-Carboxylate

Methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate was prepared following a previously reported procedure [10]. Methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (0.16 mmol, 1 eq) was dissolved in 5 mL of chloroform ($CHCl_3$) in a 20 mL round-bottom flask. Separately, freshly prepared adduct solution **3a-c** was obtained by mixing precursor **1a** or **1b** (0.14 mmol, 2.6 eq) with a tetrabutylammonium salt (0.86 mmol) in 5 mL of $CHCl_3$. The resulting adduct solution was then transferred to the round-bottom flask at room temperature. The reaction mixture was sonicated to ensure homogeneity and subsequently stirred at 60 °C for 4-48 h. After completion of the reaction, the solvent was evaporated under reduced pressure to yield a crude solid. Purification by column chromatography used a 90:10 hexane/ethyl acetate.

Methyl 2-chloro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **7a** 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (31.2 mg, 0.16 mmol), **1b** (165 mg, 0.14 mmol) and tetrabuyl ammonium chloride (240 mg, 0.86 mmol) gave **7a** (28 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.3 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 6.7 Hz, 2H), 4.11 (d, J = 17.1 Hz, 1H), 3.82 (s, 3H) and 3.57 (d, J = 17.9 Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) 195.1; matched previous report [10].

Methyl 2-azido-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **7b** 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (31.2 mg, 0.16 mmol), **1b** (149 mg, 0.14 mmol) and tetrabutyl ammonium azide (246 mg, 0.86 mmol) gave **7b** (33 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 3.81 (s, 3H), 3.68 (d, J = 17.3 Hz, 1H) and 3.05 (d, J = 17.4 Hz, 1H). Matched previous report [10].

Methyl 2-bromo-1-oxo-2,3-dihydro-1H-indene-2-carboxylate **7c** 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (40.6 mg, 0.21 mmol), **1b** (165 mg, 0.14 mmol) and tetrabutyl ammonium bromide (278 mg, 0.86 mmol) gave **7c** (19 mg, 33%). 1H NMR (400 MHz, CDCl3) δ 7.88 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.51–7.45 (m, 2H), 4.23 (d, J = 18.4 Hz, 1H), 3.84 (s, 3H) and 3.69 (d, J = 18.1 Hz, 1H). Matched previous report [10].

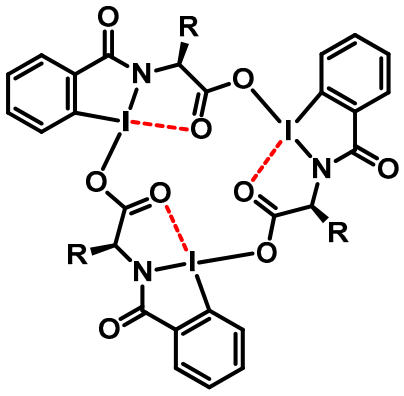
2.3. Chiral Column Separation

A Chiralpak IB N-5 (particle size 5 µm, 250 × 4.6 mm ID) column equipped with the IB N-5 guard column was used to perform chiral separations of compounds. HPLC-grade hexane and isopropanol (99:1) were used as the mobile phase. Samples were dissolved in the same solvent mixture and 10 µL was injected from the sample vial into the system. Separation was run at 1.0 mL/min.

3. Results

Our group synthesized amino acid-based hypervalent iodine macrocycles (HIMs) [11] **1a** and **1b** and confirmed the structure by NMR spectroscopy, mass spectrometry and X-ray crystallography (Figure 1) [12–14]. Upon the addition of tetra butyl ammonium (TBA) salts of fluoride, chloride, bromide, azide and cyanide to an HIM, the anion selectively bound to the iodine center, resulting in the disassembly of the HIM trimer into a distinct

HIM monomer (Figure 2). This new species was identified as a tetracoordinated HIM monomer, where iodine bound to the anion via an iodine–halogen bond. The formation of the monomer upon the addition of TBA(Cl) was further confirmed by obtaining the single crystal that was solved using X-ray diffraction (Figure 2) [12]. From the X-ray analysis, we observed one adduct per tetrabutylammonium cation.



1a R = *i*-Pr
1b R = Bn

Figure 1. Hypervalent iodine macrocycles (HIMs) prepared from amino acid-based benziodazoles. Dashed line represents the secondary bonding character. (adapted from Refs. [11,12]).

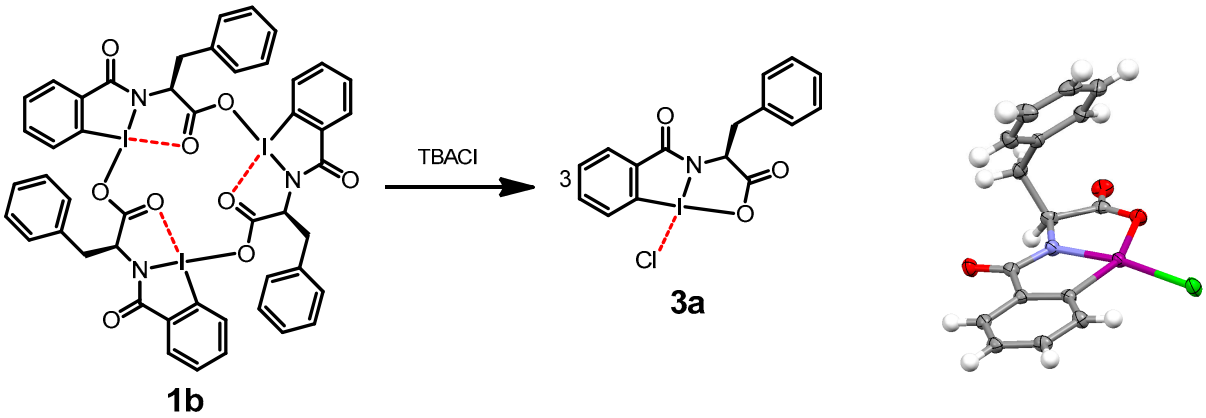
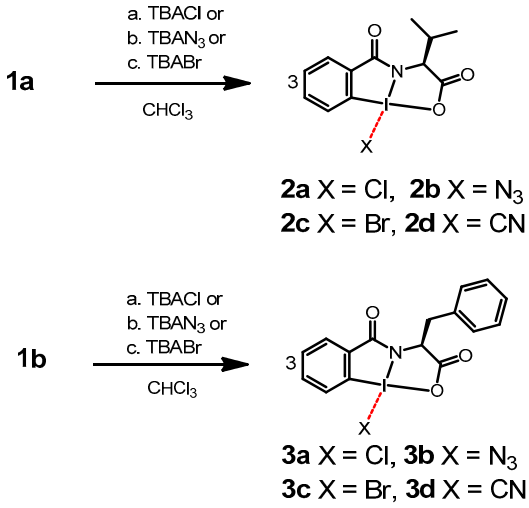


Figure 2. (**Left**) Formation of tetracoordinated hypervalent iodine adduct upon the addition of tetrabutylammonium chloride to HIMs in chloroform. (**Right**) Crystal structure of adduct with tetrabutyl ammonium cation removed for clarity. Dashed line represents the secondary bonding character (adapted from Ref. [12]).

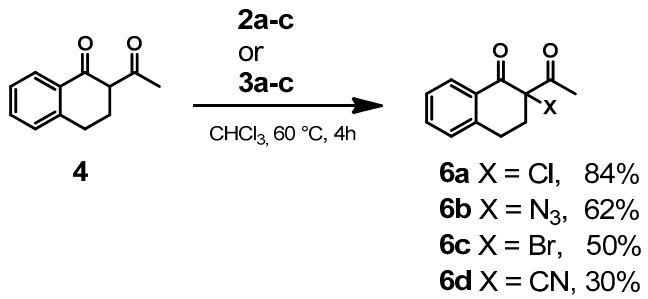
During the preliminary investigations of the anion-coordinated system, it was observed that the macrocycle could be reformed upon the addition of a coordinating metal such as silver nitrate. The chloride anion was removed from the hypervalent iodine system as a precipitate of silver chloride. Building upon this observation of the addition and removal of anions, respectively, we hypothesized that anion-coordinated HIM monomers could be used to directly transfer the anion to the alpha carbon of beta keto esters. In addition, the chiral nature of the reagent suggested asymmetric induction may be possible. Other TBA salts including TBA-Br and TBA-N3 were found to lead to similar adducts including **2a**–**c** and **3a**–**c** (Scheme 1).



Scheme 1. (**Top**) Synthesis of adduct **2a**–**d** from Val HIM **1a**. (**Bottom**) Synthesis of adduct **3a**–**d** from Phe HIM **1b**. Dashed line represents the secondary bonding character.

Past reports have shown benziodoxol(on)e-based hypervalent iodine reagents can be used to transfer azide, cyanide and acetylene onto 1,3-dicarbonyl compounds [9,10]. With this precedent and our previous results regarding reversibility in the HIM system (Figure 2), we were motivated to explore our own adduct to investigate its ability to transfer halogens and azides to the carbon center in 1,3-dicarbonyl compounds. We further hypothesized that if the iodine center in adducts remained in a chiral environment, direct chlorination, bromination and azidation could be achieved with some enantioselectivity.

To test our hypothesis, we initially chose 2-acetyl-1-tetralone (**4**) and methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**5**) as model substrates to establish the direct chlorination reaction with adduct **2a** (Scheme 2). Upon reaction of **4** in chloroform at 60 °C with **2a**, successful formation of the chlorinated product **6a** (56%) was observed within 4 h (Table 1, entry 4). For initial screening of the reaction, chloroform was used as a solvent as macrocycles **1a** and **1b** were stable in chloroform, a fact supported by the successful isolation of single crystals of the macrocycle from chloroform in previous experiments. The reaction was performed at 60 °C, based on our separate experiments that revealed compounds **1a** and **1b** decomposed when maintained at temperatures higher than 60 °C for a prolonged duration. Furthermore, reactions at room temperature did not lead to appreciable product (Table 1, entry 3). To ensure that the chloride transfer was enabled by adduct **2a**, a control experiment was performed between the 2-acetyl-1-tetralone in the presence of tetrabutylammonium chloride in chloroform at 60 °C for 4 h and no reaction was observed (Table 1, entry 2).

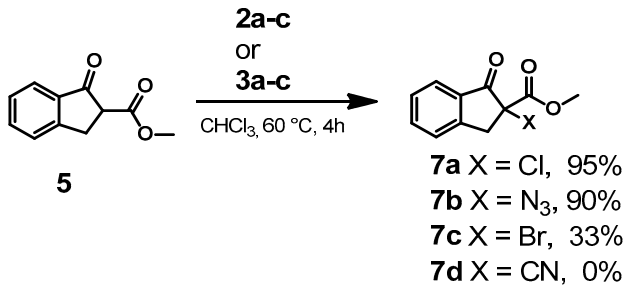


Scheme 2. Transfer of anions from hypervalent iodine adducts **2a**–**c** or **3a**–**c** to 2-acetyl-1-tetralone.

Table 1. Reaction optimization (The bold is to describe the compound number).

Entry	HIM	Salt	Substrate	Adduct (Equivalent)	Solvent	Time	Temp	Yield (%)
1	none	TBA-Cl	**4**	none	Chloroform	4 h	60 °C	none
2	none	TBA-Cl	**5**	none	Chloroform	4 h	60 °C	none
3	1b	TBA-Cl	**4**	**3a** (1.3)	Chloroform	4 h	RT	none
4	1b	TBA-Cl	**4**	**3a** (1.3)	Chloroform	4 h	60 °C	56
5	1b	TBA-N_3	**4**	**3b** (1.3)	Chloroform	4 h	60 °C	60
6	1b	TBA-Br	**4**	**3c** (1.3)	Chloroform	4 h	60 °C	40
7	1a	TBA-Cl	**4**	**2a** (2.6)	Chloroform	48 h	60 °C	84
8	1a	TBA-N_3	**4**	**2b** (2.6)	Chloroform	48 h	60 °C	62
9	1a	TBA-Br	**4**	**2c** (2.6)	Chloroform	48 h	60 °C	50
10	1a	TBA-CN	**4**	**2d** (2.6)	Chloroform	48 h	60 °C	30
11	1b	TBA-Cl	**5**	**3a** (2.6)	Chloroform	22 h	50 °C	76
12	1b	TBA-N_3	**5**	**3b** (2.6)	Chloroform	22 h	50 °C	90
13	1b	TBA-Br	**5**	**3c** (2.6)	Chloroform	22 h	50 °C	33
14	1b	TBA-CN	**5**	**3d** (2.6)	Chloroform	22 h	50 °C	0
15	1a	NaCl	**4**	**2a** (2.6)	DMSO/H_2O	22 h	50 °C	65
16	1a	NaBr	**4**	**2c** (2.6)	DMSO/H_2O	48 h	60 °C	16
17	1a	NaN_3	**4**	**2b** (2.6)	DMSO/H_2O	48 h	60 °C	20

With this initial success, other anion-based adducts were employed. For example, the reaction of **4** with **2b** and **2c** in chloroform at 60 °C for 4 h yielded azide and bromide products **6b** and **6c** with 60% and 40% yield, respectively (Table 1, entries 5 and 6). We investigated other substrates such as methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate **5** for the anion transfer (Scheme 3). Our results showed that the reaction between **5** and **2a–c** or **3a–c** also resulted in the desired anion-transferred products with a moderate to good yield (Table 1, entries 11–13). To optimize conditions, we screened the reactions in different equivalents of adducts **2a–c** or **3a–c** as shown in Table 1. When 1.3 equivalents of the adduct (from both **1a** and **1b**) were used, the reactions with **4** proceeded with moderate yields of 40–60% within 4 h. However, increasing the adduct to 2.6 equivalents and extending the reaction time to 48 h led to significantly improved yields, ranging from 37 to90% for chloride, bromide and azide (Table 1, entries 7–9). The transfer of cyanide to both substrates **4** and **5** was also investigated with the optimal conditions (Table 1, entries 10 and 14). Unfortunately, the reaction was met with limited success with only 30% yield for the six-membered **6d** and no detectable product **7d** was found. Clearly, there are issues with the transfer of this ion and it is believed to be from the instability of the final product. While these reactions were successful with the TBA salt in chloroform, we were interested to know if cheaper inorganic salts such as NaCl, NaBr and NaN_3 could also be used. To utilize these salts, a DMSO and water solvent mixture was employed. While the desired product was found under these reaction conditions, the yields were considerably lower (16–20%, Table 1, entries 15–17). The poor yields observed with polar DMSO may be due to the decomposition of the hypervalent iodine reagent. This is supported by the fact that NMR samples of macrocycle **1a** or **1b**, prepared in DMSO, showed impurities after 2 days when the same sample was reanalyzed. This matches the fact that DMSO is known to be oxidized by hypervalent iodine reagents.



Scheme 3. Transfer of anions from hypervalent iodine adducts **2a**–**c** or **3a**–**c** to methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate.

The newly synthesized products were characterized by NMR spectroscopy and mass spectrometry. After confirming the purity of the products, we further explored whether the anion transfer from adducts **2a**–**c** or **3a**–**c** to substrates **4** or **5** can occur in an enantioselective manner. A chiral column was used to perform chiral separations of compounds. For a preliminary reaction of **4** with valine-based **2b**, two peaks were observed at similar retention times and of the same area and suggested that the reaction gave a 1:1 racemic mixture of compound **6b** (Supporting Information). We observed similar racemic mixtures when using other valine-based reagents **2a**–**c**. However, we observed promising results in case of phenylalanine-based reagents. As an example, modification of **4** with **3a** led to a non-racemic mixture with an enantiomeric excess (e.e.) of 26% (Figure 3). This experiment confirmed that the transfer of anions from tetracoordinate hypervalent iodine based adducts to beta keto esters can proceed in a mildly enantioselective manner. While the e.e. was not exceedingly high, it suggested larger non-natural amino acids that could provide a larger steric field around the reaction site and could provide even better control of the enantioselectivity.

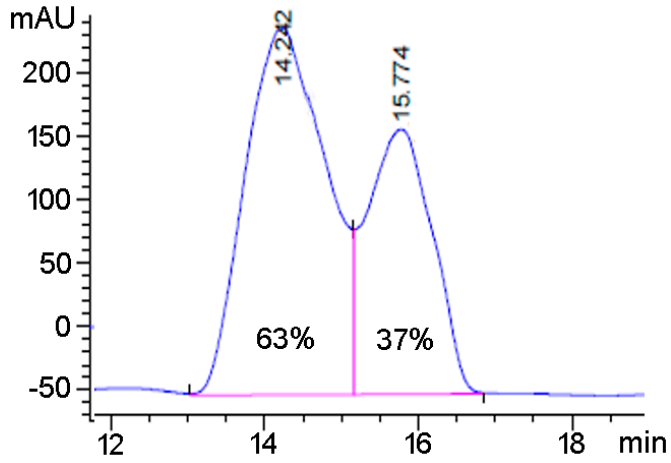


Figure 3. Chiral chromatogram of enantioenriched **6a** upon functionalization with **3a**. Percentage listed is the enantiomeric excess based on Area1: 21,039, Area 2: 12,305.

4. Conclusions

In conclusion, we have demonstrated a direct transfer of anions from an anion-associated hypervalent iodine reagent. Specifically, these freshly prepared adducts were employed to facilitate anion transfer within the 2-acetyl-1-tetralone and methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate. The anion transfer from the phenylalanine–HIM adducts was achieved in a mildly enantiomerically selective manner and suggested tuning of the sterics around the reagent could lead to better selectivities.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/org6040052/s1, Chiral HPLC of **6b** prepared from **2b**, and **6a** prepared from **2a**, NMR of compounds.

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Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author(s).

Conflicts of Interest: The authors declare no conflicts of interest.

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